In the Specification

Please amend page 1, line 3, by inserting the following:

-- This application is a filing under 35 U.S.C. 371 of international application number PCT/GB2003/004573, filed October 24, 2003, which claims priority to application number 0224799.7 filed October 25, 2002, in Great Britain, the entire disclosure of which is hereby incorporated by reference.--

Please amend page 5, by replacing the paragraph beginning on line 23 with the following paragraph:

Suitable biological targeting peptides of the present invention are 3-20 mer peptides (ie. peptides comprising 3 to 20 amino acids), preferably 4 to 15-mer, most preferably 5 to 14-mer such fragments. The peptides may be cyclic or linear or combinations thereof. The peptides may be of synthetic or natural origin, but are preferably synthetic. Such peptides include:

- somatostatin, octreotide and analogues,
- laminin fragments eg. YIGSR (SEQ ID. 1), PDSGR (SEQ ID. 2), IKVAV (SEQ ID. 3), LRE (SEQ ID. 4) and KCQAGTFALRGDPQG (SEQ ID NO. 5),
- N-formyl peptides for targeting sites of leucocyte accumulation,
- fragments of platelet factor 4 (PF4),
- RGD-containing peptides,
- peptide fragments of α_2-antiplasmin, fibronectin or beta-casein, fibrinogen or thrombospondin, which are substrates for the enzyme transglutaminase (Factor XIIIa). The amino acid sequences of α_2-antiplasmin, fibronectin, beta-casein, fibrinogen and thrombospondin can be found in the following references: α_2-antiplasmin precursor [M.Tone *et al.*, J.Biochem, 102, 1033, (1987)]; beta-

casein [L.Hansson *et al,* Gene, 139, 193, (1994)]; fibronectin [A.Gutman *et al,* FEBS Lett., 207, 145, (1996)]; thrombospondin-1 precursor [V.Dixit *et al,* Proc. Natl. Acad. Sci., USA, 83, 5449, (1986)]; R.F.Doolittle, Ann. Rev. Biochem., 53, 195, (1984).

Please amend page 7, by replacing the paragraphs beginning on line 4 with the following paragraphs:

Preferred biological targeting peptides of the present invention are 3 to 20-mer peptide fragments of α_2-antiplasmin or casein, most preferably 4 to 15-mer, especially 5 to 14-mer such fragments. Preferred α_2-antiplasmin or casein peptides of the present invention comprise at least one metabolism inhibiting group, and an amino acid sequence taken from the N-terminus of either:

(i) α_2-antiplasmin,

i.e. NH_2-Asn-Gln-Glu-Gln-Val-Ser-Pro-Leu-Thr-Leu-Thr-Leu-Leu-Lys-OH (SEQ ID. 6) or variants of this in which one or more amino acids have been exchanged, added or removed such as:

NH_2-Asn-Gln-Glu-Gln-Val-Ser-Pro-Leu-Thr-Leu-Thr-Leu-Leu-Lys-Gly-OH, (SEQ ID. 7)

NH_2-Asn-Gln-Glu-Ala-Val-Ser-Pro-Leu-Thr-Leu-Thr-Leu-Leu-Lys-Gly-OH, (SEQ ID. 8)

NH_2-Asn-Gln-Glu-Gln-Val-Gly-OH; (SEQ ID. 9) or

(ii) casein

ie. Ac-Leu-Gly-Pro-Gly-Gln-Ser-Lys-Val-Ile-Gly (SEQ ID. 10).

Especially preferred α_2-antiplasmin peptides of the present invention are peptide fragments comprising the 4 amino acid sequence Asn-Gln-Glu-Gln (SEQ ID. 11) (NQEQ). Most especially preferred such α_2-antiplasmin peptides have the sequence:

Asn-Gln-Glu-Gln-Val-Ser-Pro-Xaa-Thr-Leu-Leu-Lys-Gly (SEQ ID. 12),

where Xaa is Tyr or I-Tyr (ie. iodo-tyrosine).

Such preferred α_2-antiplasmin peptides preferably have metabolism inhibiting groups at both the peptide termini, where the aza-diaminedioxime is one of the metabolism inhibiting groups. In that instance, the aza-diaminedioxime chelator is preferably attached at the carboxy terminus, and the N-terminus is protected by a metabolism inhibiting group, preferably N-acetyl so that the α_2-antiplasmin peptide is preferably:

Ac-Asn-Gln-Glu-Gln-Val-Ser-Pro-Xaa-Thr-Leu-Leu-Lys-Gly (SEQ ID. 12),
where Xaa is Tyr or I-Tyr (ie. iodo-tyrosine).

Please amend page 24, by replacing the paragraph beginning on line 25 with the following paragraph:

When the biological targeting moiety is a peptide fragment of α_2-antiplasmin, a preferred kit formulation comprises: the ligand of Formula (I), stannous reductant, an acetate salt of a biocompatible cation, a diphosphonic acid transchelator plus a pH-adjusting agent. A preferred such kit comprises: the ligand of Formula (II); stannous chloride; sodium acetate; MDP or a biocompatible salt thereof; a radioprotectant, especially PABA or a biocompatible salt thereof, most especially the sodium salt of PABA; and sodium bicarbonate as the pH-adjusting agent. A most preferred such kit further comprises the ligand of Formula II, where each R^1 is CH_3, $(A)_p$ is NH and Z is Ac-Asn-Gln-Glu-Gln-Val-Ser-Pro-Xaa-Thr-Leu-Leu-Lys-Gly[-](SEQ ID. 12), where Xaa is Tyr or I-Tyr, and Ac is N-acetyl.

Please amend page 25, by replacing the paragraph beginning on line 4 with the following paragraph:

In a fourth aspect, the present invention provides a method of diagnostic imaging of thrombi using the radiopharmaceuticals of the present invention, where the biological targeting molecule is a 3 to 20-mer peptide fragment of α2-antiplasmin. Preferably, the

peptide fragment of α2-antiplasmin comprises the sequence Asn-Gln-Glu-Gln (SEQ ID. 11). Most preferably the peptide fragment of α2-antiplasmin comprises the sequence Asn-Gln-Glu-Gln-Val-Ser-Pro-Xaa-Thr-Leu-Leu-Lys-Gly (SEQ ID. 12), where Xaa is as defined above. Pulmonary emboli (PE) are composed of significant amounts of fibrin, which is cross-linked and stabilised by the action of Factor XIIIa. Both fibrin and Factor XIIIa are generated from non-active precursors specifically at sites of thrombosis. The peptide fragments of α2-antiplasmin of the present invention are potent substrates for Factor XIIIa, and are thus covalently bound to fibrin within pulmonary emboli *via* the action of this enzyme. The ^{99m}Tc-complexes of the aza-diaminedioxime α2-antiplasmin peptide fragment conjugates of the present invention are thus selectively taken up at the site of the embolus *in vivo*, giving positive uptake or "hot-spot" imaging for such sites relative to normal tissue. Similar logic applies to other types of thrombi *in vivo* (eg. deep vein thrombosis or dvt), since Factor XIIIa functions in a similar way. Hence, the Factor XIIIa substrate conjugates of the present invention are useful for the imaging of thrombi *in vivo*, especially pulmonary emboli and deep vein thrombosis.

Please amend page 29, by replacing the paragraphs beginning on line 1 with the following paragraphs:

Example 2: Synthesis of the Peptide Ac-NQEQVSPY(3I)TLLKG (SEQ ID. 13) (Compound 2).

The protected peptide Ac-Asn(Trt)-Gln(Trt)-Glu(OtBu)-Gln(Trt)-Val-Ser(tBu)-Pro-Tyr(3I)-Thr(tBu)-Leu-Leu-Lys(Boc)-Gly-OH (SEQ ID. 13) was assembled on a 2-chlorotrityl resin by anchoring Fmoc-Gly- to the resin, and then successive deprotections/coupling
cycles with the appropriate protected amino acids and the coupling reagents DCC and HOBt. Solid phase peptide synthesis is described in as described in P. Lloyd-Williams, F. Albericio and E. Girald; *Chemical Approaches to the Synthesis of Peptides and Proteins*, CRC Press, 1997. The terminal asparagine was acetylated, cleaved from the

resin using 0.5 % TFA and Compound 2 used without further purification as the trifluoroacetate salt.

Example 3: Synthesis of Compounds 3 to 7.

The protected Ac-NQEQVSPY(3I)TLLKG (SEQ ID. 13) peptide (Compound 2) was cleaved from the solid phase resin as described in Example 2, and then coupled with Compound 1 in solution using PyBOP (benzotriazole-1-yl-oxytris-pyrrolidino-phosphonium hexafluorophosphate) and HOBt (1-hydroxybenzotriazole) as the coupling agents. Compound 3 was obtained by deprotection in reagent K [reagent K is 82.5% TFA, 5% phenol, 5% processed water, 5% thioanisole, 2.5% ethanedithiol (EDT)]. The crude conjugate was first purified by RP-HPLC using TFA followed by a second purification and salt exchange with acetic acid, lyophilisation, filtration with a 0.22μ filter and a final lyophilisation to give Compound 3.

Molecular weight by MS 1970 ± 1 Daltons.

The peptides used in Compounds 4 and 5 were prepared in a similar manner. Compound 7 was prepared by derivatisation of Compound 1 (Pn216) with glutaric anhydride in DMF. Compound 6 was prepared by reaction of Compound 1 (Pn216) with benzoic anhydride in acetonitrile, in the presence of triethylamine.

Please insert at the end of the written description, page 37 before the claims, page 38, the "Sequence Listing" attached hereto.